REMARKS/ARGUMENTS

The non-final Office Action dated 02/25/05 rejected claims 20-21 and 30-31. Claims 1,7, 13-21 and 30-31 were pending in the case. The examined and rejected claims are those of Group IV, elected without traverse on October 28, 2004. Claims 1, 7, 13-19 were therefore assumed to be withdrawn from consideration. No claim was allowed. By this Amendment, the withdrawn claims are cancelled without prejudice, leaving claims 20, 21, 30 and 31 remaining for examination in response to the present Amendment and Response.

Turning now to the Detailed Action, the following remarks are set forth and responded to in the same order as presented in the Office Action.

Signature on response

The Office Action notes that Lennart Olsson signed the previous response as assignee. Enclosed herewith is a Power of Attorney and Change of Correspondence Address to the address for the attorney signing below.

Objections to the specification

The first paragraph has been amended to indicate the status of the applications.

The typographical error is Table 2 has been corrected. Please see the definition of (pepIR) at page 25, line 9. It intends the internalization sequence derived from the insulin receptor.

Introductory Remarks

Before discussing the substantive objections and rejections, some discussion concerning the claimed invention is considered warranted. Present claims 20, 30 and 31 require a comparison to minimize the effect of artifacts.

In claim 20 one is comparing the activity of a candidate bioactive agent with a cell having a mutated internalization sequence "wherein the ability of said cell surface receptor to internalize in response to ligand binding is altered by said modification." It does not matter what the specific modification is of the internalization sequence, so long as the internalization upon binding of ligand to the receptor is altered. What one is determining by the claimed assay is whether a change in internalization resulting from the presence of the candidate bioactive agent is as a result of binding at the internalization sequence or binding at some other site. Since the cell surface comprises numerous proteins to which the candidate bioactive agent may bind, the outcome of such binding can give a spurious result. By comparing the effect of the agent on a cell that has an incompetent internalization sequence and a competent internalization sequence, one subtracts out effect associated with other than the binding of the agent to the internalization sequence.

Claim 21 is broader in that it does not include the comparison and would be subject to a spurious result that could be corrected by performing the assay of claim 20.

Claim 30 requires, at a minimum, an internalization sequence of a receptor and uses the MHC sequence to compete with the candidate bioactive agent. One determines the binding of the MHC sequence in the presence and absence of the agent, so that one can determine whether the agent binds to the internalization sequence. As presently amended, some latitude is permitted for the internalization sequence.

Claims 20 and 30 have been amended, the new language concerning the molecular weight finding support on page 16, lone 16.

Rejection of Claims 20 and 30-31 under 35 USC § 112 as being indefinite

Before discussing the substantive objections and rejections, some discussion concerning the claimed invention is considered warranted. Present claims 20, 30 and 31 require a comparison to minimize the effect of artifacts.

In claim 20 one is comparing the activity of a candidate bioactive agent with a cell having a mutated internalization sequence "wherein the ability of said cell surface receptor to internalize in response to ligand binding is altered by said modification." It does not matter what the specific modification is of the internalization sequence, so long as the internalization upon binding of ligand to the receptor is altered. What one is determining by the claimed assay is whether a change in internalization resulting from the presence of the candidate bioactive agent is as a result of binding at the internalization sequence or binding at some other site. Since the cell surface comprises numerous proteins to which the candidate bioactive agent may bind, the outcome of such binding can give a spurious result. By comparing the effect of the agent on a cell that has an incompetent internalization sequence and a competent internalization sequence, one subtracts out effect associated with other than the binding of the agent to the internalization sequence.

Claim 21 is broader in that it does not include the comparison and would be subject to a spurious result that could be corrected by performing the assay of claim 20.

Claim 30 requires, at a minimum, an internalization sequence of a receptor and uses the MHC sequence to compete with the candidate bioactive agent. One determines the binding of the MHC sequence in the presence and absence of the agent, so that one can determine whether the agent binds to the internalization sequence. As presently amended, some latitude is permitted for the internalization sequence.

Claims 20 and 30 have been amended, the new language concerning the molecular weight finding support on page 16, lone 16.

Rejection of Claims 20-21 and 30 under 35 USC § 112 as failing to comply with the written description requirement

The rejection of claims 20-21 and 30 is respectfully traversed. The Examiner is respectfully directed to page 22, beginning at line 8, where the method for identification of internalization sequences is described. In Table I numerous examples are given and since the filing of this application, numerous additional examples are now known. The Examiner is respectfully directed to U.S. Patent application no. 09/991,518 for evidence in support of this statement. The bioactivity of these sequences is described on page 5, lines 9 – 18. The internalization sequences are adequately defined as being present in the extracellular portion of receptors, having a minimum similarity to a defined peptide sequence and when the peptide is present with the receptor from which it is derived, it modulates the internalization of the receptor.

So far as the reasons why the definition of the internalization sequence is inadequate, these have been avoided by amendment. The only sequence that is used for similarity determinations is SEQ ID NO:1. Secondly, the Experimental section, page 22, adequately defines how similarity is determined. Table I is testimony to the effectiveness of this approach.

The discussion in paragraph 3 is not understood. The only modifications involved are the inactivation of the internalization sequence of a receptor, so that it is non-responsiveness to the oligopeptide or an active candidate bioactive compound. This has been discussed above. Otherwise, the sequence that could be modified is now specified as being the wild-type internalization sequence when used in the method of claim 30.

The summation paragraph is submitted to be no longer applicable, since the sequence to which that paragraph is directed is SEQ ID NO:1. Finally, it is one of the surprises of this invention that despite using a single sequence for the determination of the internalization sequences of receptors, each of the internalization sequence fits the algorithm used, while being substantially different from each other. It is respectfully submitted that the 10 examples is ample proof of the potency of this approach.

Rejection of Claims 21 and 30 under 35 USC §102(b) as being anticipated by Olsson et al. WO 95/05189

Turning now to the rejections of 35 USC §102, the rejection of claims 21 and 30 based on Olsson (WO 95/05189) is respectfully traversed. It should be noted that Olsson was not aware that there was an internalization peptide that could be used for performing assays. Rather the reference cited by the Examiner, believed that it was the binding of the MHC sequence to the receptor that was necessary. At that time, there was no appreciation that one could prepare a portion of the native receptor as determined in accordance with the subject application and that oligopeptides would modulate internalization. The Examiner errs in equating the natural sequence derived from the receptor and the MHC sequence used to find the natural sequence.

The second basis is avoided by amendment as the bioactive peptide is now the wild-type internalization sequence derived from the receptor. The Examiner states "The 'oligopeptide used by Olsson et al (page 20, lines 10 – 13; this page seemed incorrect and page 19 was taken for comment) corresponds to the instant 'receptor-derived oligopeptide' used in steps a) and b) of instant claim 30." In rebuttal, it should be mentioned that the belief was that two receptors became bound to initiate internalization. There is no suggestion that there was a sequence specific for this purpose and that is the sequence was prepared as an oligopeptides, it would be active. The MHC derived oligopeptide should not be confounded nor conflated with the receptor derived oligopeptides. When one is unaware of the existence of a substance and if such substance exists, does not know how it may be discovered, there can be no anticipation or

obviousness. That is the situation here. The MHC sequence proved to be the Rosetta stone for discovering the internalization sequences of receptors, but it was not appreciated at the time of the Olsson reference.

It is not a matter that the steps of the assays are the same in the reference and claim, a key reagent unknown at the time of the reference was not known. This is particularly cogent in the case of claim 20, where one inactivates the internalization sequence of the receptor. This was unimaginable at the time of the Olsson reference as it was not known that there was such sequence, nor was it known how to find such sequence.

So far as claim 21, absent any knowledge of the internalization sequence at the time of the reference, claim 21 cannot be anticipated.

As to inherency, it is submitted that the Examiner errs in his finding of inherency. As discussed above, while the MHC sequence and the receptor internalization sequences have some similarity—that was how the receptor internalization sequences were found—they are different, each being derived from different proteins, but sharing a common activity.

So far as claim 31, it is now correctly dependent on claim 30 and for the reasons given above also avoids the rejection on Olsson. The query concerning SEQ ID NO:1 has been clarified. Unfortunately, the sequence number of the reference was carried into this application.

Rejection of claims 21 and 30 under 35 USC § 102(f) and (g) Olsson et al. 5,639,548 and 5,865,888

This rejection corresponds to the rejection above, noting that there are different inventive entities on the cited US patents and the subject application.

Response

The rejections of claims 21 and 30 under 35 USC §102 (f) and (g) is respectfully traversed. It is believed that the patents cited by the Examiner, 5,639,548 and 5,865,888, are properly 5,639,458 and 5,385,888, respectively. The following arguments are based on this premise.

Both of these patents have the same disclosure as WO 95/05189. Since at the time it was believed that it was the MHC peptide that was binding and active, the present claims in requiring the sequence from the receptor cannot be anticipated. The inventors, as has been stated above, at the time of these references did not know that there were specific sequences involved with internalization as part of the receptor sequence, nor knew how they might be determined.

Rejection of claims 20-21 and 30 under the judicially created doctrine of obviousness-type double patenting

So far as the double patenting rejection, once the only impediment to issuance is the filing of an appropriate terminal disclaimer, assuming it is still appropriate for the claims allowed in this application, a terminal disclaimer would be provided.

Conclusion

Applicants request that this amendment to the claims and specification be entered and the rejections of claims 20, 21, 30 and 31 be withdrawn for the reasons advanced above. Based on the above considerations, it is submitted that all of the rejections have been successfully avoided or traversed, save for double patenting and the Examiner is respectfully requested to withdraw these rejections. In view of the amendments and remarks, the claims are considered in proper form for allowance only subject to the filing of an appropriate terminal disclaimer and the Examiner is respectfully requested to so indicate. If the Examiner believes that the prosecution

of the subject application may be expedited by a telephonic interview, the Examiner is hereby authorized to call Bertram Rowland collect at (650) 344-4674.

Respectfully submitted,

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